IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of

REIF et al.

Serial No. 10/561,800

for: Bone Formation Agent And Method Of Production

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Mail Stop Amendment
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1. I, Dr. Fabian Peters of Brunnenstraße 30, D-68259 Mannheim, a citizen of Germany, hereby declare:

- that I have a degree in chemistry having studied at the Ruprecht-Karls University in Heidelberg and at the University of Hamburg;

- that subsequent to my undergraduate degree, I worked as scientist at University of Hamburg from 1998-2001;

- that I received a Ph.D. in Chemistry at University of Hamburg in 2001 having worked at the institute of solid state chemistry at the University of Hamburg;

- that I entered the employ of Curasan AG in August 2001, where I was appointed senior scientist in the biomaterials department and was responsible for the research and development of biomaterials;

- that I subsequently became Technical Director in January 2005 and I am responsible for all research and development activities of Curasan AG;

- that I am a member of numerous work and planning groups/associations such as GDCh (German Chemical Society), German Society for Biomaterials (DGBM), Society for Biomaterials (SFB), located in Mt. Laurel, NJ/USA, Working Group Bioceramics in Aachen/Germany, Society for Thermal Analysis;

- that I have authored or co-authored 30 articles, including articles in the field of biomaterial sciences, such as:

[1] M. Epple, F. Peters, K. Schwarz, "Composite aus Polyglycolid und Calciumphosphat als potentielle Knochenersatzmaterialien" in: *Tagungsbände der Werkstoffwoche/Materialica 1998* (München 12.-15.10.1998), Band IV, Symposium 4: Werkstoffe für die Medizintechnik (H. Planck, H. Stallforth, Eds.), Wiley-VCH **1999**, S.233-237

[2] M. Epple, O. Herzberg, F. Peters, K. Schwarz, "Mikrostrukturiertes Polyglycolid als biomedizinischer Werkstoff", in: N. M. Meenen, A. Katzer, J.M. Rueger, "Zelluläre Interaktion mit Biomaterialien", Hefte zur Zeitschrift "Der Unfallchirurg" 278, Springer, Berlin-Heidelberg **2000**, S. 22-27.

[3] Fabian Peters, Karsten Schwarz and Matthias Epple, „The structure of bone studied with synchrotron X-ray diffraction, X-ray absorption spectroscopy and thermal analysis“, *Thermochimica Acta* **2000**, *361*, 131-138

[4] W. Linhart, F. Peters, W. Lehmann, K. Schwarz, M. Amling, M. Siedler, J.M. Rueger, M. Epple, „New Scaffolds for Tissue Engineering: Biocompatible Composites of Carbonated Apatite and Biodegradable Polyesters“, *Cells Tissues Organs* **2000**; *166*, 73

[5] Wolfgang Linhart, Fabian Peters, Wolfgang Lehmann, Karsten Schwarz, Arndt Friedrich Schilling, Michael Amling, Johannes Maria Rueger, Matthias Epple, „Biologically and chemically optimized composites of carbonated apatite and polyglycolide as bone substitution materials“, *Journal of Biomedical Materials Research* **2001**, *54 (2)*, 162-171

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[8] F. Peters, M. Epple, "Crystallization of calcium phosphates under constant conditions with a double-diffusion setup", *Journal of the Chemical Society, Dalton Transactions* **2002**, 3585-3592

[9] D. Tadic, F. Peters, M. Epple, "Continuous synthesis of amorphous carbonated apatites", *Biomaterials* **2002**, *23*, 2553-2559

[10] F. Peters, M. Epple, "Die Kristallisation von Calciumphosphaten unter konstanten Bedingungen mit der Doppeldiffusionstechnik", *Freiberger Forschungshefte* E3 **2002**, 104-123

[11] S. V. Dorrozkin, E. I. Dorozhkina, F. Peters, M. Epple, „In vitro simulation of calcium phosphate crystallization from modified simulated body fluid”, *Eur. J. Trauma.* **2002**, *2*, 115-116

[12] F. Peters, D. Reif, “Functional Materials for Bone Regeneration from Beta-Tricalcium Phosphate”, *Mat.wiss. u. Werkstofftech.* **2004**, *35* (4), 203-207

[13] M. Ermrich, F. Peters, X-ray diffraction structure of beta-tricalcium phosphate, PDF 2, Set 55 (**2005**), PDF 55-898, International Center of Diffraction Data, Pennsylvania, USA

[14] Duerr, H.; Peters, F.; Haenel, T.: "Patient-specific resorbable biocompatible bone substitute through 3D-Printing", In: Fraunhofer-Allianz Rapid Prototyping (Ed.): Proceedings of the International User's Conference on Rapid Prototyping & Rapid Tooling & Rapid Manufacturing Euro-uRapid2005, Leipzig, May 10th-12th **2005**, Germany

[15] Haenel, T., Peters, F. Duerr, H. “Patient-Specific resorbable biocompatible bone substitute through 3D-Printing” In: Proceedings of the FAIM´05, Flexible Automation & Intelligent Manufacturing, Bilbao, July 18^{th}-20^{th} **2005**, Spain

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[17] M. Ermrich, F. Peters, „X-ray powder diffration data of synthetic β-Tricalcium Phosphate", Mat.-wiss. u. Werkstofftech. **2006**, *37* (6), 526-529

[18] F. Peters, D. Groisman, R. Davids, Th. Hänel, H. Dürr, M. Klein, "Comparative Study of patient individual implants from β-tricalcium phosphate made by different techniques based on CT data", Mat.-wiss. U. Werkstofftech. **2006**, *37*(6), 457-461

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[23] T. Hänel, F. Peters, C. Hoffmann, H. Dürr, „Aus CT-Daten generierte patientenindividuelle Implantate aus β-Tricalciumphosphat für die Knochenregeneration", *Regenerative Medizin*, 1 (2), **2009**, 13-17

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[26] A. Bernhardt[1]*, A. Lode[1], F. Peters, M. Gelinsky; " Perfusion culture of osteogenic induced mesenchymal stem cells in β-tricalcium phosphate ceramics with large interconnective channels", *J Tissue Eng Regen Med*, **2010** (accepted)

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[28] F. Peters, A. Bernhardt, A. Lode, M. Gelinsky, „Osbone® eine neue, synthetische Biokeramik für den Knochenersatz“, *Regenerative Medizin*, 1 (3), **2010**, 18-22

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- that I am named as inventor on numerous applications/patents relating to biomaterials and my field of research and expertise is in this area of biomaterials, where I apply my scientific background in inorganic chemistry and material science.

I am the same Fabian Peters who is named as inventor of U.S. Ser. No. 10/561,800 ("the '800 application"), filed on November 13, 2006. I am familiar with the invention described in the '800 application and am familiar with its prosecution history, in particular, the final Office Action mailed on October 14, 2010, and the Advisory Action mailed on December 22, 2010.

I understand that the Examiner rejected pending claims 1, 2, 12, 13-15 and 17-20 as allegedly being obvious over a combination of DE 29922585 (DE '585), Beam (WO 02/083194) and Starling et al. US 6,210,715. Claims 3, 4, 11, 12 and 16 were rejected as allegedly being obvious over a combination of DE 29922585 (DE '585), Beam (WO 02/083194) and Starling et al. US 6,210,715 as applied to pending claims 1, 2, 12, 13-15 and 17-20, and further in view of Johansson (WO 92/21302).

Specifically, the Examiner's rejection asserts that it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the cited patents in a manner that would be readable upon or suggestive of the claimed combination of features recited in the claims. The Examiner asserts that all limitations are taught in the applied art and that individual deficiencies of the cited art are remedied by the teachings of the other cited patents. Specifically, it is repeatedly stressed that the instant rejection is a combinatorial rejection and, accordingly, one individual reference need not teach what is taught by the other references. I respectfully submit that the Examiner's assertions are incorrect, for the reasons more fully described below.

It is my opinion that the claimed bone formation agent which is composed of a combination of numerous features is not proved obvious merely by demonstrating that each of its features was, independently, known in the prior art. It is my understanding that there must be some suggestion or motivation to lead a person having skill in the art to arrive at the claimed combination of features. However, it appears to me as if the Examiner's arguments are directed to individual features of the cited references while ignoring the fact that the claimed invention as a whole is not rendered obvious for at least the reason that some of the limitations are not disclosed in the applied art and that there is also no reason offered for the suggested "routine optimization" of the specific features recited in the claims.

The amended claims in the Amendment - After Final Rejection presented herein, now read as follows:

1. (Currently amended) Bone formation agent of porous pure-phase beta-tricalcium phosphate having an isotropic sintered structure and, between the sintered particles of the calcium phosphate, statistically distributed pores in a plurality of discrete size ranges, characterised in that it has a porosity composed of at least three discrete ranges of pore sizes (I) to (III), which are statistically distributed in terms of their size, and the maxima of the three discrete pore size distributions are at pore diameters in the ranges from 0.5 to 10 μm (I), 10 to 100 μm (II) and 100 to 5000 μm (III), the porosity has an irregular geometric shape, the sintered particles of the calcium phosphate have a particle size smaller than 63 μm with a d_{50} value in the range from 5 to 20 μm, the interconnecting pore share in the porosity is limited to pore sizes less than 10 μm, and the maxima of the discrete pore size distributions (II) or (III) are a figure less than half the average granulate size of a granulate fraction and are in a range between 10 and 50 % of the average granulate size of a granulate fraction.

Support for amended claim 1 can, for example, be found in pending claims 1, 3 and 12. Support for the phrase "pure-phase" can, for example, be found at page 6, 2nd para. of the originally filed specification.

2. (Cancelled)

3. (Cancelled)

4. (Currently amended) Bone formation agent according to claim 1, characterised in that the volume shares of the discrete pore size distributions (I) to (III) are in the range from 20 to 40 % by volume for pore size distribution (I), in the range

from 5 to 40 % by volume for pore size distribution (II) and in the range from 1 to 40 % by volume for pore size distribution (III), the overall porosity not exceeding a figure of 85 % by volume.

5. (Cancelled)

6. (Previously presented) Bone formation agent according to claim 1, characterised in that the calcium phosphate consists of preferably beta-tricalcium phosphate having a phase purity of ≥ 99 % by weight, relative to the foreign hydroxyapatite phase.

7. (Previously presented) Bone formation agent according to claim 1, characterised in that it is in the form of a granulate and is present in various granulate fractions in a size range between 50 and 10000 μm.

8. (Original) Bone formation agent according to claim 7, characterised in that the granulate has a substantially non-uniform geometric shape.

9. (Original) Bone formation agent according to claim 7, characterised in that the granulate has a substantially uniform geometric shape.

10. (Original) Bone formation agent according to claim 9, characterised in that the granulate has a substantially spherical shape.

11. (Cancelled)

12. (Cancelled)

13. (Original) Bone formation agent according to claim 1, characterised in that it is in the form of a shaped body having a defined geometric design.

14. (Original) Bone formation agent according to claim 13, characterised in that in addition to a statistical porosity it has a defined porosity in the form of tubular pores.

15. (Previously presented) Bone formation agent according to claim 14, characterised in that the defined tubular porosity is formed by one-, two- or three-dimensional bores, introduced by machining, in the diameter range from 0.5 to 2 mm, and the overall porosity consisting of statistical and tubular porosity does not exceed a value of 85 % by volume.

16. (Previously presented) Bone formation agent according to claim 1, characterised in that the bone formation agent is a compact shaped body [[has]] having a pore size distribution graduated in size and volume share from the periphery to the core, with the peripheral zone pore size distributions (I) and/or (II) being present with an overall porosity of up to 35 % by volume and in the core zone pore size distributions (I) and/or (II) and/or (III) being present up to an overall porosity of 85 % by volume, with the peripheral zone having a range from 10 % to 40 % and the core zone from 60 % to 90 % of the largest dimension of the implant perpendicular to the tensile stress direction or parallel to the bending stress.

17. (Previously presented) Bone formation agent according to claim 1, characterised in that it has, on its surface and/or in its internal pore structure, antibacterial, wound healing

promoting, bone growth-promoting and/or anticoagulant substances in suitable effective concentrations.

18. (Previously presented) Bone formation agent according to claim 13, characterised in that it has a shape individually made for a particular patient.

19. (Previously presented) Bone formation agent according to claim 13, characterised in that it is present in standardised dimensions and shapes, preferably in the form of a cube, cuboid, cylinder or wedge.

20. (Previously presented) Bone formation agent according to claim 13, characterised in that it has an indication-related shape in the form of a trepanation closure, alveolar augmentation or filler for cages for vertebrae replacement.

21. - 32. (Withdrawn)

Insofar as the rejections may apply to the amended claims, I respectfully submit that the prior art does not teach or suggest the invention as claimed.

I understand that the Examiner maintains the obviousness rejection because the Examiner believes that a skilled artisan would have had a reasonably high expectation of successfully arriving at the claimed invention and would also have been particularly motivated by the prior art teachings to modify them according to the claimed invention. I disagree.

It is not contested that numerous bone substitutes comprising calcium phosphate are known in the art. However, the prior art does not teach or suggest the invention as claimed.

The Claimed Invention

The claimed bone regeneration material has to fulfill a placeholder function, i.e. to degrade during formation of new bone while avoiding to disintegrate into small particles that can provoke inflammatory reactions. Initially, I would like to draw Examiner's attention to the following features of the claimed invention:

(a) the bone formation agent consists of porous pure-phase beta-tricalcium phosphate;

(b) the bone formation agent is characterized by three discrete pore size distributions, namely pore size distributions (I), (II) and (III);

(c) the sintered primary particles of the calcium phosphate have a particle size smaller than 63 μm with a d_{50} value in the range from 5 to 20 μm;

(d) the interconnecting pore share in the porosity is limited to pore sizes less than 10 μm;

(e) the maxima of the discrete pore size distributions (II) or (III) are a figure less than half the average granulate size of a granulate fraction and are in a range between 10 and 50 % of the average granulate size of a granulate fraction.

The claimed material shows significant improvements over heretofore known materials which advantageous effects are directly attributable to the above combination of features (a) to (e).

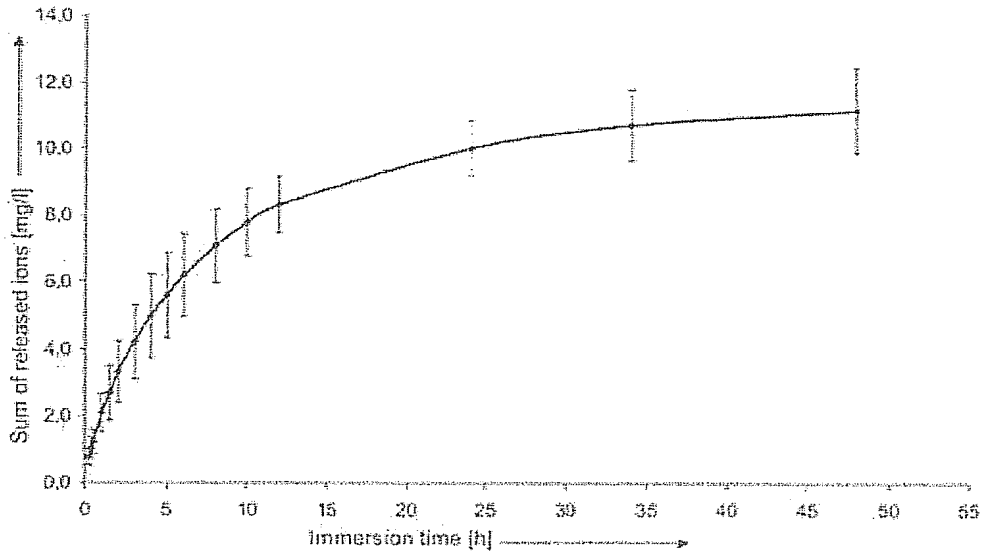
First, the importance of feature (a), i.e. phase purity, is that the material is more stable and differences in resorption and /or degradation of the material can be avoided. Calcium phosphates exist in numerous phases that differ in thermodynamic stability and solubility. For instance, hydroxyapatite is the thermodynamically most stable and most insoluble calcium phosphate and therefore not biodegradable. These phase transitions are dependent on both time and temperature and can readily occur during the sintering process. Additionally, the different phases have a different volume and thermal expansion coefficient, and hence, the microstructure of mixed phase calcium phosphates is instable due to overstressing and cracking.

I enclose as attachment I the article of Bauer and Hohenberger, cfi/Ber. DKG 66, Causes of Behavioral Variation of Bioactive Calcium Phosphate Ceramics in Living Organisms (1989). Figure 4 of this article shows the phase diagram with the various existing modifications of calcium phosphate at high temperatures and Figures 1 and 2 show the different stability of the calcium phosphate phases. At page 26, the volume surge and different thermal expansion coefficients are discussed, which induce microstructural stresses and cracking in mixed phase calcium phosphates.

Second, the claimed material shows full biodegradation as a result of the combination of features (a), (b), (c) and (e). In particular, feature (e) assures that the specific surface

of the claimed material is uniform thereby resulting in a constant material to solution ratio and a homogeneous resorption. This is demonstrated by a BET solubility measurement, the results of which are shown in Fig. 1 below.

Fig. 1: Solubility measurement



Third, the claimed material shows improved osteointegration and osteoconductivity as a result of the combination of features (a), (b), (c) and (e).

Notably, heterogeneous materials, i.e. non-phase pure materials, decompose during chemical degradation and biological resorption into small particles which trigger inflammatory reactions. Additionally, osteoconduction is hampered, since fibrous tissue can grow into the defect and prevent bone healing. Phases with higher stability, e.g. hydroxyapatite, are, moreover, not fully resorbed.

Fourth, the claimed material shows sufficient mechanical stability, while possessing a high porosity as a result of the combination of features (a), (b), (c), (d) and (e). The improved mechanical stability is mainly due to the combination of features (b), (c) and (d). As a result of this improved stability, decomposition into smaller subparticles is prevented and the risk of inflammatory reactions is significantly reduced.

Fifth, the importance of feature (d) is that an invasion of macropores by germs is prevented (see, page 8, 2nd para. and page 9, 3rd para. of the instant specification). The problem of infections which ultimately leads to the loss of the implant is a general problem of synthetic ceramics that has so far not been satisfactorily solved (see, for example, attachment I, page 23, "ceramic porosity").

I enclose as attachment II the article of Palm, Implants 7, Cerasorb M – a new synthetic pure-phase β-TCP ceramic material in oral and maxillofacial surgery (2006), where the claimed material has been tested in 121 patients. This article summarizes the advantageous effects of the claimed material over hitherto known bone substitutes. Specifically, the results of this study show that the claimed combination of features leads to a material with enhanced mechanical stability and improved bone regeneration due to its unique interconnective open multiporosity (features (b) and (d) and (e)) and its granule size and structure (feature (c)). Its special multiporosity produces an enhanced capillary effect and thus ensures cell nutrition and resorption from within the granules. Additionally, the material is fully resorbed and does not degrade or disintegrate into small particles provoking inflammatory reactions. Above all, the problem of

infections which cannot be treated with antibiotics as reported by Palm with respect to alternative materials (cf. page 2, 1st para.) does not occur with the claimed material.

Also enclosed as attachment III is the cover page of the article by Weibrich et al., Z Zahnärztl. Implantol. 16, Charakterisierung der Oberflächenmorpholgie von Knochenersatzmaterialien mittels REM [Characterization of the surface morphology of bone regeneration materials via SEM] (2000). As can be taken from the abstract of this article, the shape of the particles, their surface structure, and the porosity are critical and important factors that influence the resulting osteoconductivity, degradation characteristics, and the risk for bacterial contamination.

The Rejections

DE'585 teaches a temporary bone defect filler with a microporous and macroporous structure, wherein the micropores form a portion of 10 to 50% and the macropores form a portion of 50 to 90% of the total porosity. Moreover, DE'585 differentiates between

(i) partially interconnecting macropores which make up **50-90%** of the total porosity; and
(ii) noninterconnecting adjacent macropores connected via the cell walls by micropores.

Thus, DE'585 does at least not teach or suggest features (b), (c), (d) and (e) of the instant invention. However, as discussed above, the specific combination of features is essential to achieve the advantageous effects of the claimed material. For instance, the particle size according to feature (c) has been selected to provide a **strong ceramic bond** in the sintered particles due to stable sintering necks, which

provides an additional safeguard to prevent inflammatory reactions (also referred to as foreign-body reactions).

It is respectfully submitted that even a combination of DE'585 with Beam and Starling does not cure the deficiencies of DE'585.

Beam relates to engineered regenerative biostructures. The biostructures have resorbable and non-resorbable regions. The biostructures Beam describes contain hydroxyapatite (Beam, p. 2, lines 24-26 and examples), micropores having a median pore size between 10 to 15 microns (Beam, Claim 2) and interconnecting mesoporosity and/or macroporosity (Beam, p. 7, lines 9-19 and p. 11, lines 9-21 and Figures 16 and 19). Notably, Beam confirms that degradation products of some classes of material can activate inflammatory responses and that matching porosity and internal architecture to specific tissue response remains an unmet challenge. Thus, a skilled artisan would clearly recognize that even minor modifications in the choice of the specific calcium phosphate modification employed, its purity, pore size distribution, porosity, particle size, particle shape etc. are critical factors that influence the characteristics of the material.

All in all, Beam fails to teach or suggest the claimed combination of features (a)-(e). In fact, Beam is at least entirely silent with respect to the specific individual features (a), (c), (d), and (e) of the claimed invention. Thus, a combination of DE'585 and Beam at least fails to teach or suggest the combination of features (c), (d) and (e) of the claimed invention.

Starling et al. relates to hollow calcium phosphate microbeads or microspheres and their use in cell culturing systems, chromatography and implantable biomedical materials. Starling describes CaP microspheres for chromatographic applications ranging in size from about 10 μm to about 100 μm, with open porosity in the range of about 20% to about 60% and a pore size range from about 0.01 to about 0.5 μm (Starling, Col. 8, lines 44-48, and Figure 1.8). Starling does also describes microspheres for use as a biomedical implant having a size range of about 500 μm to about 1000 μm and an interstitial open porosity of about 60% with a pore size range of about 350 μm to about 500 μm (Starling, Col. 8, line 58 to Col. 9, line 5).

There is no teaching or suggestion, however, that these calcium phosphate microbeads would be of pure-phase beta-tricalcium phosphate. There is also no teaching or suggestion of three discrete pore size distributions, an interconnecting pore share in the porosity limited to pore sizes less than 10 μm, or that the maxima of the discrete pore size distributions (II) or (III) are a figure less than half the average granulate size of a granulate fraction and are in a range between 10 and 50 % of the average granulate size of a granulate fraction.

Thus, Starling et al. at least fails to teach or suggest features (d) and (e) of the claimed invention. Starling et al. does also not provide any motivation, teaching or suggestion for a material having the combination of features recited in amended claim 1.

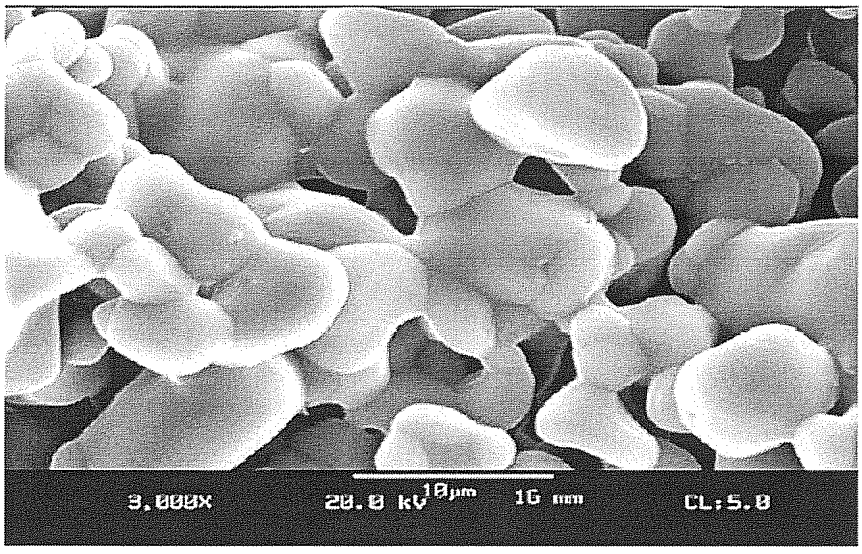
Furthermore, a simple change of the sintering temperature as suggested by the Examiner as "routine optimization" would not lead to the claimed invention. One of skill in the art would readily recognize that changes in sintering temperature would result in a heterogeneous material due to phase transitions (e.g. to alpha-TCP) and at the same time the pores would

collapse resulting in a product lacking pore size distributions (II) and (III)as seen in Figure B below.

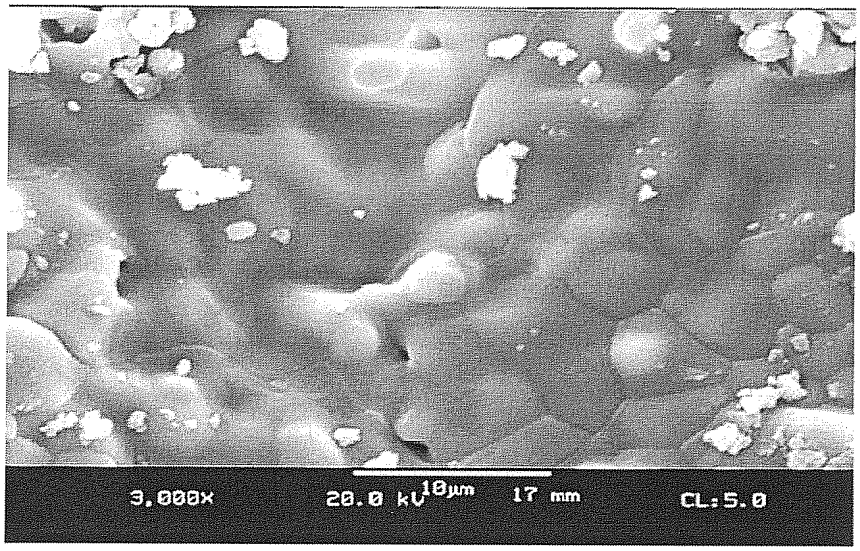
Thus, modifying the sintering temperature according to Starling et al as suggested in the Action would lead to a dense product of mixed phase calcium phosphates that does neither possess the claimed phase-purity nor the claimed porosity and pore size distribution. The challenge of the instant invention was to find a product that due to its unique design provides maximal mechanical stability, highest porosity with specific pore size distribution, and highest phase purity.

The differences between the claimed material and a product of DE'585 modified by changing the sintering temperature and time to produce a more highly closed porosity composition with fewer and smaller interconnecting pores is shown in images A and B below. Image A shows the bone formation agent according to the invention. Image B shows a product of DE'585 obtained by modifying the sintering temperature as suggested by the Action and allegedly disclosed in Starling et al.

A Calcium phosphate bone formation agent according to the invention.



B Calcium phosphate after more complete sintering to obtain a more dense composition with smaller pore sizes.



The product represented in Figure B is a mechanically extreme stable but nearly non resorbable material (caused by the extremely elongated solution velocity by a small inner surface) that contains also other calcium phosphate phases due to the modified sintering conditions.

Thus, a combination of DE'585, Beam and Starling et al. does not teach or suggest the claimed invention for at least the reason that none of these documents teaches or suggests a material having a porosity of an irregular geometric shape, and an interconnecting pore share in the porosity limited to pore sizes less than 10 μm. Since the behavior of the material is strongly dependent on the specific combination of features, a skilled artisan would have had no reason to conclude that the claimed material would indeed be superior. The differences between the prior art materials and the claimed material are discussed in detail above, and therefore one of ordinary skill in the art would recognize that the cited references would not

be readable upon or suggestive of the specific combination of features of the claimed invention. In fact, all references are directed toward a material with an interconnecting macroporosity, and hence show completely different characteristics in relation to stability, resorption, solubility, osteoconductivity, osteointegration, and inflammatory responses.

It is my firm opinion that there is no reason offered from either DE'585, Beam, Starling or any other reference cited, alone or in combination, that would motivate a person skilled in the art to arrive at the claimed invention. Again, there is no reason offered in the respective teachings to select the use of the specific combination of features recited in amended claim 1, especially not the absence of any interconnecting meso- and macropores, as the necessary element to be modified; one of ordinary skill in the art could have tried any number of other elements for modification (e.g. different calcium phosphate, different pore volume, different pore sizes, unimodal or bimodal distribution of pore sizes rather than three different pore sizes, different particle size, etc) such that rather than a finite number of solutions, there was an infinite number of solutions for a bone formation agent.

For any of the above reasons, I do not agree with the Examiner`s belief about the reasonable expectation of a skilled artisan in view of the state of the art. In my opinion, one of ordinary skill in the art would have had no reason to conclude that the claimed bone formation agent, which (as opposed to the applied art) employs a specific, porous calcium phosphate having no interconnecting meso- and/or macropores, would result in a material that shows improved stability, fully resorbs, and is advantageous with

respect to the suppression of inflammatory responses, despite its high porosity and in view of the details the prior art supplies in describing the advantages of interconnecting meso- and/or macropores.

In particular, I am of the opinion that the rejection is based on hindsight, since, lacking the instant invention as a blueprint, there is no reason offered in the respective teachings or from the generally available knowledge as to why the particular claimed combination of features should be selected for a bone formation agent.

It is my position that the present invention, against all expectations, especially in the light of the applied prior art, surprisingly shows that it is possible to provide a bone formation agent that overcomes limitations of the prior art and provides additional benefits. Again, the applied art nowhere teaches or suggests the specific combination of features recited in amended claim 1 and provides no apparent reason to specifically select and modify certain features recited in amended claim 1 to arrive at the claimed invention.

In view of the remarks to the applied art presented herein, it is my opinion that the Examiner's obviousness rejections should be reconsidered and withdrawn for all of the pending claims in the subject application. Claim 1 is patentable for at least the reasons described above. Claims 4, 6-10, and 13-20 add further limitations to claim 1. Therefore, claims 4, 6-10, and 13-20 are likewise patentable.

The undersigned further declares that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and

the foregoing statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 08 APR. 2011

By: _____

Fabian Peters, Ph.D.

Encl.

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Dr. Gerd Bauer

Ursachen des unterschiedlichen Verhaltens von bioaktiven Calciumphosphatkeramiken im Organismus

Causes of behavioral variation of bioactive calcium phosphate ceramics in living organisms

G. Bauer/G. Hohenberger

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Einleitung

In der Humanmedizin hat sich Al_2O_3-Keramik als Implantatwerkstoff wegen seines inerten Verhaltens im Organismus sehr gut bewährt. Seit einigen Jahren kommen bioaktive Werkstoffe, für den Knochenersatz hinzu. Wegen ihrer Reaktivität wird diese Substanzklasse, in Abhängigkeit von der Zusammensetzung und der Anwendungsform (Blockmaterial oder Granulat), in der BRD als Arzneimittel behandelt.

Definition der Bioaktivität

Bioaktive Werkstoffe für den Knochenersatzbereich verwachsen direkt mit dem Knochen ohne Bindegewebsschicht dazwischen. Die Einheilung erfolgt beschleunigt.

Die eigentliche Ursache der Bioaktivität für den Knochenersatzbereich ist bis heute nicht verstanden; sie wird aber mit der Anwesenheit oder der Bildung von Calciumphosphat in der Keramik, dem Glas oder der Glaskeramik zurückgeführt.

Der Knochen besteht selbst aus 70% Mineralphase, 22% organischer Matrix und 8% Wasser (1). Die Mineralphase des Knochens ist Hydroxylapatit, $Ca_5(PO_4)_3OH$ (HA). Allerdings entspricht die Zusammensetzung nicht der Stöchiometrie: das Ca/P-Verhältnis liegt zwischen 1.5 und 1.67 und es werden deutliche Mengen von Nebenelementen gefunden: hauptsächlich Na^+, K^+ und Mg^{2+} im Kationenteilgitter, Carbonat- und Sulfationen anstatt Phosphat und F^- anstelle der Hydroxylgruppe. Die Summe der „Verunreinigungen" liegt über 5%.

Tierexperimentell bzw. klinisch getestete Calciumphosphatkeramiken

Bisher wurden folgende Stöchiometrien auf ihre biologische Verträglichkeit getestet (2):

	Chem. Formel	oxidisch	Ca/O-Verh.
Ca-Metaphosphat	$Ca(PO_3)_2$	$CaO\ P_2O^5$	0.5
Di-Ca-Phosphat	$Ca_2P_2O_7$	$2\,CaO\ P_2O_5$	1.0
Tri-Ca-Phosphat	$Ca_3(PO_4)_2$	$3\,CaO\ P_2O_5$	1.5
Hydroxylapatit	$Ca_5(PO_4)_3OH$	$10\,CaO{\cdot}3\,P_2O_5{\cdot}H_2O$	1.67
Tetra-Ca-Phosphat	$Ca_4(PO_4)_2O$	$4\,CaO\ P_2O_5$	2.0

Alle 5 Ca-Phosphatkeramiken wurden als bioaktiv eingestuft, d.h. der direkte Kontakt zum Knochen wurde gefunden. Da man jedoch eine erhöhte Zahl von Makrophagen („Freßzellen") beim Ca-Metaphosphat und dem Di-Ca-Phosphat feststellte, kamen diese beiden Keramiken nicht in die klinische Erprobung. Klinisch relevant sind heute nur Tricalciumphosphat (TCP) und Hydroxylapatit (HA).

Dabei gilt TCP überwiegend als resorbierbar und HA als resorptionsresistent. Kompliziert wurde die Lage dann allerdings dadurch, als sich herausstellte, daß es auch TCP-Keramiken gibt, die praktisch keine Resorptionserscheinung zeigen, während manche HA-Präparate im Organismus hohe Resorptionsraten aufweisen.

Porosität der Keramik

Mit Hilfe von Tierversuchen konnte ermittelt werden, daß der Organismus in der Lage ist, in poröse Keramik einzusprossen, falls der durchge-

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Introduction

Thanks to their inert behavior in the human body, Al_2O_3 ceramics serve well as medical implants. In the course of the past few years, Al_2O_3 has been joined by a number of bioactive materials serving as bone substitutes. Due to the reactivity of such substances, the entire category is treated as pharmaceutics in the Federal Republic of Germany, with subclassification depending on the composition and method of application (as block material or granulate).

Definition of bioactivity

Used as bone substitutes, bioactive materials bond directly to the bone, with no connective tissue forming in between. Incorporation is accelerated.

Even today, no one fully understands the real cause of osteogenic bioactivity, but it is generally ascribed to the presence or formation of calcium phosphate in the ceramic, glass or glass-ceramic material.

Human bones consist of 70% mineral phase, 22% organic matrix and 8% water [1], with the mineral phase being composed of hydroxylapatite, $Ca_5(PO_4)_3OH$ – (HA). The composition, however, is not stoichiometric: the Ca/P ratio is situated between 1.5 and 1.67, and significant amounts of accessory elements are present (mainly Na^+, K^+ and Mg^{2+} in the cation sublattice, carbonate and sulfate ions instead of phosphate, and F^- in place of the hydroxyl group. Total "impurities" add up to more than 5%.

Animal-experimentally and/or clinically tested calcium phosphate ceramics

The following stoichiometries have been tested for biocompatibility [2]:

	Chem. formula	Oxidic	Ca/P ratio
Ca-metaphosphate	$Ca(PO_3)_2$	$CaO\ P_2O^5$	0.5
Di-Ca-phosphate	$Ca_2P_2O_7$	$2\,CaO\ P_2O_5$	1.0
Tri-Ca-phosphate	$Ca_3(PO_4)_2$	$3\,CaO\ P_2O_5$	1.5
Hydroxylapatite	$Ca_5(PO_4)_3OH$	$10\,CaO{\cdot}3\,P_2O_5{\cdot}H_2O$	1.67
Tetra-Ca-phosphate	$Ca_4(PO_4)_2O$	$4\,CaO\ P_2O_5$	2.0

All 5 Ca-phosphate ceramics were rated as bioactive, i.e. direct ceramic-to-bone contact was observed. Since, however, an increased number of macrophage cells were detected in the case of Ca-metaphosphate and Di-Ca-phosphate, those two ceramics were not included in the clinical testing program. As of this writing, only tricalcium phosphate (TCP) and hydroxylapatite (HA) have achieved clinical relevance.

TCP is generally regarded as resorbable, while HA counts as resorption-resistant. The situation was complicated by the fact that some TCP ceramics were found to show practically no resorptive capacity, while some of the HA preparations displaced high in-vivo resorption rates.

Ceramic porosity

It was determined by way of animal studies that the organism is able to intergrow porous ceramic material with a minimum continuous pore diameter of 100 µm. If the ceramic material is bioactive, such interaction will culminate in a form of osseous integration marked by the overgrowth of living bone onto the ceramic.

Continuous porosity, i.e. pores with no constrictions, is difficult to achieve, constituting a technological problem that has not yet been

hende Porendurchmesser von 100 µm eingehalten wird. Bei bioaktiver Keramik kommt es in diesem Fall zu einer knöchernen Integration mit Aufwachsen von lebendem Knochen auf die Keramik.
Die durchgehende Porosität ohne Einschnürung der Poren stellt ein technologisches Problem dar, das bei (synthetischen) Keramiken noch nicht zufriedenstellend gelöst werden konnte. Klinisch muß jedoch ein interkonnektierendes Porensystem ohne Einschnürungen gefordert werden, da es andernfalls zu Infektionen im Keramikblock kommen kann. Dies führt unabänderlich zum Verlust des Implantats.
Das geforderte Porensystem wird heute in einem Großteil der Fälle durch einen Kunstgriff erzeugt: Anstelle der porösen Keramikblöcke verwendet man dicht gesintertes, abgerundetes Keramikgranulat. Die gewünschte Porosität erhält man durch das Haufwerk der Granulatschüttung.
Diese Technik wird sehr erfolgreich, z.B. für den Aufbau des Kieferkamms nach vorausgegangener Resorption infolge von Zahnlosigkeit, eingesetzt:
Dazu werden 2 kleine Einschnitte in die Kieferschleimhaut angebracht, danach wird die Knochenhaut vom Kieferknochen abgehoben. In den entstehenden Tunnel wird das Keramikgranulat mit Hilfe einer Spritze eingebracht. Wegen der ausgezeichneten Verträglichkeit der Keramik kommt es im Verlauf von einer Woche zum Einsprossen des Gewebes in das Granulat, so daß der Kieferaufbau palpatorisch bereits fest ist. Die endgültige Prothese kann bereits nach 5–6 Wochen angepaßt werden.
Es sei angemerkt, daß es sich beim Kieferkammaufbau in der Regel nicht um eine Knochenneubildung handelt, sondern um einsprossendes, derbes Bindegewebe.
Dagegen kommt es bei Einsatz dieser Implantate im Knochen zur knöchernen Integration.

Wirkung von TCP-Keramik

Beim Kieferkammaufbau wird ein Implantatwerkstoff gewünscht, der keinerlei Resorptionserscheinungen mehr zeigt, denn es war bereits die Resorption des Knochens vorausgegangen. Dagegen wären für fast alle übrigen denkbaren Anwendungen bioaktive Keramiken wünschenswert, die kontrolliert resorbiert und anschließend durch vitalen Knochen ersetzt werden.
Dies wird in der Tat bei den resorbierbaren Calciumphosphatkeramiken beobachtet.
Damit scheint sich ein alter Wunschtraum zu erfüllen, denn wir besitzen zum ersten Mal in der Geschichte der Medizin einen anorganischen Implantatwerkstoff, der direkt mit dem Knochen verwächst; der sich im Organismus auflöst und dabei durch lebenden Knochen ersetzt wird.
Die Freude wurde jedoch getrübt, als man begann, den Ursachen der Resorption nachzugehen. Dabei zeigte sich, daß viele TCP-Keramiken in wäßrigen Lösungen eine ausgeprägte Alterung aufwiesen, und daß im Organismus ein regelrechter Partikelzerfall eintritt. Die daraufhin einsetzende Inkorporation der Partikel durch Makrophagen veranlaßte De Groot (3) zu der generellen Warnung vor der Verwendung von poröser TCP-Keramik, da eine Anhäufung der Makrophagen in den Lymphknoten und die Möglichkeit derer Entartung zu befürchten sei. Dies hat wiederum dazu geführt, daß in der BRD der Einsatz von TCP-Keramik als Implantatwerkstoff fast vollkommen eingestellt wurde.

Grundlagen

Um einen besseren Einblick in die ablaufenden Mechanismen zu erhalten, wurden Grundlagenuntersuchungen im System der Calciumphosphate und Analysen der Rohstoffe aller erhältlichen Präparate durchgeführt.
Von der Vielzahl der Calciumphosphate ist unter üblichen Bedingungen in wäßrigen Lösungen oberhalb von pH 6.3 nur Hydroxylapatit beständig. Allerdings deckt er ein sehr breites Band in der Zusammensetzung ab, so daß das Ca/P-Verhältnis von ca. 1.3 bis über 4 reichen kann. Damit kann unter anderem ein Pulver im Ca/P-Verhältnis wie TCP gefällt werden, während die Mineralphase des HA gefunden wird. Das bedeutet, daß eine Kontrolle des Phasenbestands gefällter Pulver keine Aussage über die Zusammensetzung zuläßt.
Bei der Erhitzung der Pulver wird jedoch eine Zersetzung des HA ab ca. 800 °C beobachtet. Abweichend von Beobachtungen De Groots (4), bildet sich jedoch aus HA entsprechend der exakten Stöchiometrie bei Ca-Defizit eine Mischung aus HA und TCP, bei Ca-Überschuß oberhalb von ca. 1300 °C HA und Tetra-Calciumphosphat (s. Abb. 1)* bzw. unterhalt von 1300 °C HA und CaO. HA zersetzt sich bei üblichen Luftfeuchtigkeit-

*) °C – Angaben in Bild 1 !

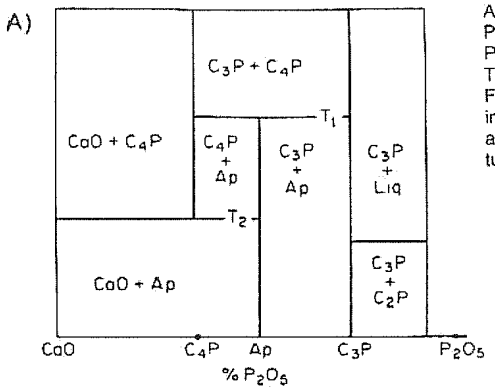

Abb. 1: Stabilität der Phasen im System CaO – P_2O^5 als Funktion der Temperatur
Fig. 1: Stability of phases in the system CaO – P_2O^5 as a function of temperature

satisfactorily resolved for synthetic ceramics. In clinical terms, however, an interconnecting system of unpinched pores is necessary, because the ceramic block could otherwise become a source of infection, and that would certainly lead to loss of the implant.
The requisite system of pores is now usually achieved with a trick: instead of using porous ceramic blocks, the implants are used as dense-sintered, rounded-off ceramic granulate. The desired porosity is then provided incidentally by the cavities in the package of the spheres. This approach yields very good results for the augmentation of the alveolar ridge after resorption due to the loss of teeth.
This entails making two small incisions in the mucous membrane of the jaw and then lifting the periosteum away from the jawbone. The ceramic granulate is introduced into the resultant tunnel with the aid of a syringe. Thanks to the excellent biocompatibility of the ceramic material, new tissue grows into the granulate within a week, thus yielding a jaw structure that is already firm to the touch. The final prosthesis can be adapted after 5 or 6 weeks. It should be noted that the augmentation of the alveolar ridge does not usually involve the neoformation of real bone, but rather the intergrowth of hard connective tissue. When such implants are used in bones, though, the result is osseous integration.

Effects of TCP-base ceramic material

The implant material needed for the augmentation of the alveolar ridge should ideally exhibit not resorption phenomena whatsoever, since resorption of the bone has already taken place. By contrast, bioactive ceramics would be desirable for practically all other applications requiring controlled resorption and, subsequently, substitution by vital bone. Such is the case with resorbalbe calcium phosphate ceramics. An age-old dream seemed to have come true in that we finally had at our command, for the first time in the history of medicine, an inorganic implant material that would bond directly to the bone, gradually being resorbed by the organism and replaced by living bone.
Then, the question of what causes the resorption was looked into and the findings damped some of the enthusiasm: many types of TCP ceramics proved to age so quickly in aqueous solutions, that virtual disintegration of the ceramic into particles takes place within the organism. The resultant incorporation of the particles by macrophage cells prompted De Groot [3] to issue a general warning against the use of porous TCP ceramics, because the accumulation of macrophages in the lymphatic nodes and their potential degeneration has to be taken into account. That, in turn, led to the near-complete discontinuance of using TCP ceramics as implant materials in the Federal Republic of Germany.

Fundamental principles

To gain better insight into the mechanisms involved, the system of calcium phosphates was made the subject of fundamental research, and the raw materials of all available preparations were analyzed.
Of all the many calcium phosphates, hydroxylapatite is the only one that will remain stable under normal conditions in an aqueous solution with a pH of 6.3 or higher. The basic composition, however, covers such a wide spectrum that its Ca/P ratio can range from 1.3 to above 4. Consequently, a powder with a Ca/P ratio corresponding to that of TCP can be precipitated, while the mineral phase proves to be that of HA. In other words, checking the mineral phases of a precipitated powder provides no reliable information on that powder's composition.
If the powder is heated, however, HA begins to dissociate at about 800 °C. Unlike observations made by De Groot [4] HA yields, appropriate to the exact stoichiometry, a mixture of HA and TCP for a Ca deficit,

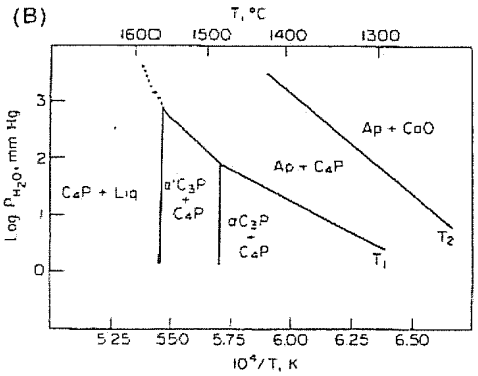

Abb. 2: Stabilität der Calciumphosphatphasen mit dem Ca/P-Verhältnis > 1.67 in Abhängigkeit vom Wasserdampfpartialdruck
Fig. 2: Stability of calcium-phosphate phases with a Ca/P ratio > 1.67 as a function of steam partial pressure

ten erst ab ca. 1400 °C (s. Abb. 2). Das heißt, bei Einhaltung der theoretischen Zusammensetzung kann auch reine HA-Keramik gesintert werden.

Die Bewertung der chemischen Zusammensetzung deckt eine weitere Schwierigkeit auf:

	% CaO	% P_2O_5	% H_2O (wt.%)
TCP	54.3	45.7	–
HA	55.8	42.4	1.8

Die Differenz im CaO-Gehalt beträgt nur 1.5%. Eine gute naßchemische Analyse hat in diesem System jedoch nur eine Genauigkeit von 0.3%.
Daraus ergibt sich, daß bei einem Rohstoff, der innerhalb einer guten chemischen Analytik die Zusammensetzung von HA besitzt, nach dem Erhitzen ca. 20% TCP als Zweitphase gefunden werden kann.
Dies führte in der Vergangenheit zu erheblichen Schwierigkeiten, da mit üblichen Methoden keine Unterscheidung der Rohstoffe möglich war.
Eigene Untersuchungen belegen, daß in der BRD 1985 damit begonnen wurde, die Zusammensetzung der Keramik zu korrigieren. Inzwischen ist jedoch auch der Rohstoff mit einer maximalen TCP-Konzentration nach Erhitzen auf der Nachweisgrenze von ca. 1% zu erhalten.
Für die klinische Praxis bedeutet diese Aussage allerdings, daß in der Vergangenheit die Präparate in der Zusammensetzung stark geschwankt haben, und bis heute sind noch nicht alle Produkte auf dem Stand der Technik.

Ablauf der Resorption

Bisher wurde über die ablaufenden Mechanismen der Resorption gerätselt; insbesondere wurde vielfach davon ausgegangen, daß sich die chemischen Löslichkeiten von TCP und HA sehr stark unterscheiden, so daß unterstellt wurde, daß TCP deshalb wesentlich schneller in Lösung geht.
Die chemische Löslichkeit ist primär abhängig vom Löslichkeitsprodukt. Im Organismus steht das Blut, das in Temperatur, Druck und pH praktisch keinen Schwankungen unterliegt, im Gleichgewicht mit der Oberfläche des Skeletts. Aus der bekannten Oberfläche der Mineralphase des Knochens läßt sich eine Gesamtoberfläche von weit über 1 km² an Calciumphosphat im menschlichen Körper berechnen. Damit muß das Blut im gesunden Organismus an Calcium- und Phosphationen gesättigt sein.

Aus der unterschiedlichen Löslichkeit von TCP und HA ist unter diesen Umständen nur abzuleiten, daß TCP oberflächlich in HA umgewandelt wird. Dies ist in der Tat nachweisbar (5).
Damit kann die chemische Löslichkeit nicht als Erklärung für das unterschiedliche Verhalten im Organismus herangezogen werden. Ähnliches gilt für die biologische Löslichkeit, unter der zusätzliche Reaktio-

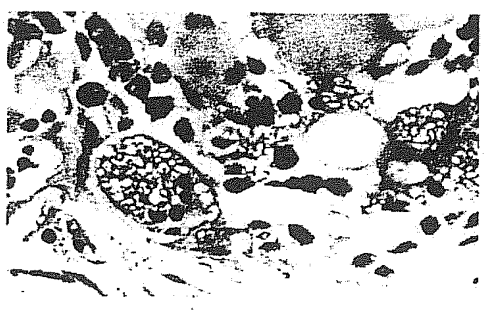

Abb. 3: Mehrkernige Riesenzelle (Makrophage), beladen mit Keramikpartikeln. (Dunkel = 4 Zellkerne in der Riesenzelle) Donath [6]
Fig. 3: Polynuclear giant cell (macrophage) loaden with ceramic particles (dark = 4 nuclei in the macrophage cell) Donath [6]

HA and tetracalcium phosphate for excessive Ca (above 1300 °C; cf. fig. 1; note temperatures in °C) or HA and CaO below 1300 °C. At normal humidity levels, HA does not dissociate below about 1400 °C (cf. fig. 2). This means that even pure HA ceramics can be sintered if the theoretical composition is adhered to.
Evaluation of the chemical composition exposes another problem:

	% CaO	% P_2O_5	% H_2O (wt.%)
TCP	54.3	45.7	–
HA	55.8	42.4	1.8

While the difference in CaO content amounts to only 1.5%, a good wet-chemical analysis of this system can only be expected to be accurate within 0.3%.
Accordingly, a raw material displaying the chemical composition of HA within the limits of a good chemical analysis can be expected to contain up to 20% TCP as secondary phase after heat treatment.
In the past, this has engendered substantial difficulties, because standard methods did not suffice to distinguish between different raw materials.
The author's own studies document the fact that work on correcting the ceramic's composition was begun in the Federal Republic of Germany in 1985. As of this writing, however, a raw material with a maximum TCP concentration of about 1% (after heat treatment before detection) is available.
As far as clinical practice is concerned, this means that the preparations used to have very divergent compositions; even now, not all products reflect the state of the art.

The process of resorption

The mechanisms responsible for resorption have been the object of much guesswork; for one thing, it was widely assumed that the chemical solubility of TCP differed greatly from that of HA, thus leading to the postulation that TCP therefore dissolves much more quickly than HA.
However, chemical solubility is primarily a function of the solubility product. The organism's blood, which is subject to practically no variation in temperature, pressure or pH, is in a steady state with the surfase area of the skeleton. The known surface area of the skeleton's mineral phase can be used for calculating the total surface area (far in excess of 1 km²) of the calcium phosphate in an adult human body. Obviously, a healthy person's blood *must* be saturated with calcium ions and phosphate ions. Under the circumstances, then, the only conclusion to be drawn from the difference between the solubilities of TCP and HA is that TCP can be converted into HA at the surface. Indeed, that is a provable fact [5]. Observed differences in in-vivo behavior therefore cannot be attributed to differences in the chemical solubility of the implant material. This also applies by analogy to biological solubility, meaning such additional reactions as complexing via amino acids or the hormonal control of the calcium level by the two hormones calcitonin and parathormone. With regard to the steady state, complexation equilibria are only complementary. The surface area should play a part in hormonal controlled resorption: since the surface area of the ceramic material is minute in comparison to that of the bone's mineral phase, the ceramic material should remain extensively intact.
The histological evidence establishes the existance of two other mechanisms: cell-mediated resorption and the incorporation of particles by giant cells (macrophage cells).
The human skeleton is subject to a continuous series of metaplastic processes, during which bones are transformed in accordance with the given physiological requirements. Consider, for example, the effects of dental braces: the pressure exerted by the braces results in bone being resorbed on one side and new bone forming on the other.
The human body employs two special kinds of cells for carrying out metaplastic processes: Those which dissolve unwanted bone (osteoclasts) and those which serve as bone-forming cells (osteoblasts).
It was quite clearly demonstrated that – especially in the case of Ca-phosphate ceramic material embedded in connective tissue – the osteoclasts are activated, i.e. they dissolve the ceramic enzymatically as if it were bone.
While that contribution toward resorption is unequivocally demonstrable, information presently available indicates that it plays only a subordinate role.
Most resorption occurs due to disintegration of the ceramic material along its grain boundaries, followed by incorporation of the individual particles by macrophage cells (cf. fig. 3) [6]. The fact should be emphasized that this constitutes a normal biological function, since any

nen, wie z.B. die Komplexierung mittels Aminosäuren, aber auch die hormonelle Steuerung des Calciumspiegels über die beiden Hormone Calcitonin und Parathormon verstanden sein sollen. Die Komplexierungsgleichgewichte sind nur eine Ergänzung bezüglich des Lösungsgleichgewichts. Bei der hormonellen Umsetzung sollten die Oberflächen eingehen: Da Keramik im Vergleich zu der Mineralphase des Knochens eine Oberfläche hat, die um viele Potenzen geringer ist, dürfte Keramik auf diesem Wege fast nicht angegriffen werden.
Die histologischen Befunde weisen 2 andere Mechanismen nach: Die zellvermittelte Resorption und die Inkorporation von Partikeln durch Riesenzellen (Makrophagen).
Das Skelett steht ständig in Umbauvorgängen, bei denen entsprechend der physiologischen Anforderungen der Knochen umgeformt wird. Als Beispiel seien Zahnspangen genannt, bei denen unter dem Druck der Spangen der Knochen auf einer Seite resorbiert und auf der anderen Seite neu gebildet wird.
Für diese Umbauvorgänge besitzt der Organismus 2 spezialisierte Zellarten: Die knochenabbauenden (Osteoklasten) und knochenaufbauenden (Osteoblasten) Zellen. Es konnte sehr deutlich gezeigt werden, daß vor allem an Ca-Phosphat-Keramik, die im Bindegewebe zu liegen kommt, die knochenabbauenden Zellen tätig werden, das heißt, sie lösen enzymatisch die Keramik auf, als sei sie Knochen. Dieser Beitrag der Resorption ist eindeutig nachweisbar, spielt jedoch nach allem, was bisher bekannt ist, eine untergeordnete Rolle.
Der Hauptresorptionsweg verläuft dagegen über den Zerfall der Keramik entlang der Korngrenzen und anschließende Inkorporation der Körner durch die Makrophagen (s. Abb. 3) (6). Es sei betont, daß auch dies eine übliche biologische Funktion ist, denn treten bei einem Knochenbruch Knochensplitterchen auf, die in einer vergleichbaren Größenordnung wie die Zellen liegen, so greifen ebenfalls die Makrophagen nach demselben Mechanismus ein.

Ursachen für den Partikelzerfall

Es konnte nachgewiesen werden, daß sich TCP- und HA-Keramiken in der Neigung zum Partikelzerfall unterscheiden; dafür konnten die folgenden Gründe gefunden werden:

1. „Auflösung an den Hälsen":
Auf diesen Mechanismus hat frühzeitig De Groot verwiesen (3). In diesem Zusammenhang sei darauf verwiesen, daß zur Erhöhung der Resorptionsneigung meist poröse TCP-Keramiken eingesetzt wurden und daß häufig nur sehr niedrig gebrannt wurde, damit die Poren während des Sinterns nicht kollabieren. Damit kamen mechanisch nicht belastbare Keramiken in den Handel, die teilweise schon in Wasser zu Pulver zerfallen. Auch HA-Keramiken wurden vereinzelt angeboten, die gleich schlecht sind und daher resorbiert werden. D.h. zu niedrig gebrannte Calciumphosphatkeramiken neigen generell zum Zerfall im Organismus.

2. Volumensprung beim Phasenwechsel α-/β-TCP
TCP liegt nach dem Phasendiagramm (s. Abb. 4) oberhalb von 1125 °C als α-TCP, darunter als β-TCP vor. Da üblicherweise oberhalb dieser Temperatur gesintert wird, kommt es bei der Abkühlung zum Phasenwechsel, der einen Volumensprung von 7.3% bis Raumtemperatur beinhaltet. Vergleicht man diese Zahl mit den 0.8% Volumenänderung beim gefürchteten Quarzsprung (573 °C) in Porzellan, so wird verständlich, daß es im Gefüge zu Spannungen und Rissen kommen muß, falls man diesem Phänomen nicht mit geeigneten sintertechnischen Maßnahmen begegnet.

3. Thermischer Ausdehnungskoeffizient
Dilatometermessungen (s. Abb. 5) bestätigten nicht nur den Volumensprung während der Phasenumwandlung sondern ergaben auch, daß die thermischen Ausdehnungskoeffizienten von α- und β-TCP nicht zueinander passen:

α-TCP	$60 \times 10^{-6}K^{-1}$
β-TCP	$13.1 \times 10^{-6}K^{-1}$
HA	$11.6 \times 10^{-6}K^{-1}$

Geht man davon aus, daß die Differenz der thermischen Ausdehnungskoeffizienten kleiner als 15% sein sollte, ergibt sich, daß α-TCP neben β-TCP oder HA Risse und Spannungen im Gefüge induziert. Es sei darauf hingewiesen, daß die Phasenumwandlung von TCP stark temperatur- und zeitabhängig ist: laut Dilatometermessung findet die Umwandlung über einen Temperaturbereich von mehreren hundert Kelvin statt

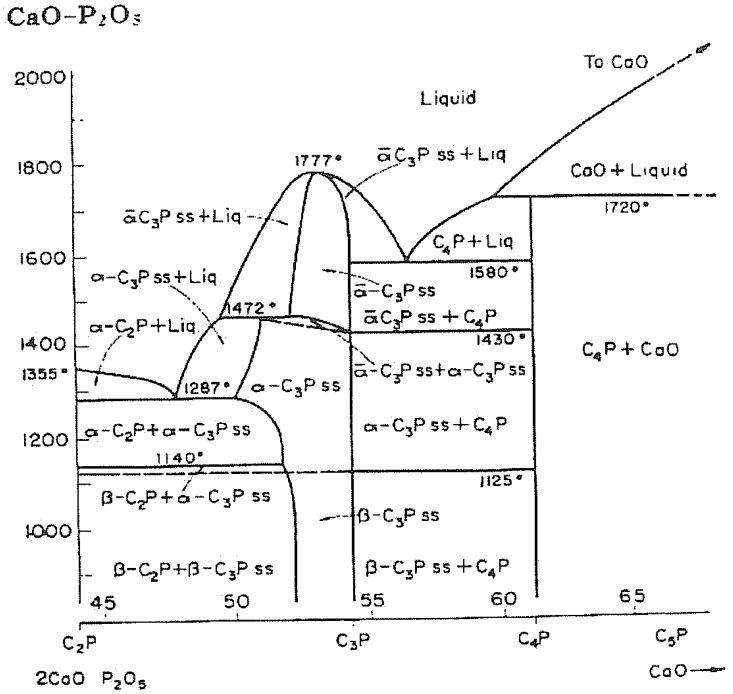

Abb. 4: Phasendiagramm CaO – P_2O^5 im Bereich des TCP
Fig. 4: Region of TPC in the CaO – P_2O^5 phase diagram

chips and splinters resulting from a comminuted fracture are also attacked by macrophage cells as part of the same mechanism, as long as the chips and splinters are of a size comparable to that of the cells.

The causes of particle disintegration

If was demonstrated that TCP- and HA-base ceramics differ in their inclination toward particle disintegration. The following reasons were found:

1. "Dissolution at the necks"
De Groot [3] was early to call attention to this mechanism. It should be noted that porous TCP ceramics were given preference with a view to the resorption tendency. Additionally, many of the ceramics were fired at very low temperatures in order to keep the pores from collapsing as a result of sintering. This led to the marked appearance of mechanically weak ceramics that sometimes even tended to disintegrate to powder in contact with water. Even some HA-base ceramics were made available – which were of equally poor quality and, hence, resorbable. In other words, excessively low-fired calcium phosphate ceramics generally tend to disintegrate in the human body.

2. Volume surge upon α-/β-TCP phase transition
As indicated by the phase diagram (cf. fig. 4), TCP occurs as α-TCP obove 1125 °C and as β-TCP at lower temperatures. Since sintering normally occurs above 1125 °C, cooling to room temperature therefore results in phase transition and a consequent 7.3% decrease in volume. Comparing that figure with the 0.8% change in volume resulting from the dreaded quartz surge at 573 °C in porcelain, one can readily accept the fact that suitable techniques must be employed to counter that phenomenon in connection with the sintering process. Otherwise, the microstructure will be subject to overstressing and cracking.

3. Thermal expansion coefficient
Dilatometric measurements (cf. fig. 5) not only confirmed the volume surge during phase transition, but also showed that the thermal expansion coefficients of α-TCP and β-TCP do not match:

α-TCP	$60 \times 10^{-6}K^{-1}$
β-TCP	$13.1 \times 10^{-6}K^{-1}$
HA	$11.6 \times 10^{-6}K^{-1}$

Proceeding on the assumption that the difference between the coefficients of thermal expansion should amount to less than 15%, it follows that α-TCP in company with β-TCP or HA must induce microstructural stresses and cracking. Attention is called to the fact that the phase transition of TCP is heavily dependent on both time and temperature: accord-

und in Röntgendiffraktometerspektren läßt sich belegen, daß übliche TCP-Keramiken auch bei Raumtemperatur noch α-TCP als Zweitphase aufweisen.

4. HA-Keramik mit Calcium-Defizit

Wie bereits dargelegt, wiesen in der Vergangenheit infolge der Schwankungen der Rohstoffzusammensetzung viele Keramiken ein Ca-Defizit auf. Damit enthielt die Keramik TCP in merklichen Mengen als Zweitphase. Deshalb sind diese Keramiken jedoch im Abkühlungsschritt von Anfang an gefährdet: Die Ausdehnungskoeffizienten von α-TCP und HA passen nicht zueinander, so daß Spannungen entstehen. Hinzu kommt der Volumensprung des TCP beim Phasenwechsel. Damit sind zweiphasige HA-Keramiken stärker von einer Gefügezerrüttung gefährdet als TCP-Keramiken, da es bei phasenreinem TCP sintertechnisch einfacher ist, die Spannungen abzubauen.

5. Treibmineraleffekt

Da TCP in Wasser unter üblichen Bedingungen thermodynamisch nicht stabil ist, kommt es zur Phasenumwandlung in HA unter Wasseraufnahme. Läßt man weitere Effekte außer Acht, so errechnet sich daraus eine Volumenzunahme von 7,6%. Diese Volumenzunahme entspricht etwa d[illegible]des gefrierenden Wassers und führt zur Gefügezerrüttung. Dies steht im Einklang mit der Beobachtung, daß Ca-Phosphatkeramiken in wäßrigen Lösungen eine ausgeprägte Festigkeitsabnahme zeigen.

Isotopenversuche mit ^{45}Ca

Isotopenversuche belegten, daß im Weichgewebe und speziell in den Lymphknoten keine Anreicherung der Keramikpartikel erfolgt, so daß daraus geschlossen werden muß, daß die Keramikpartikel nach Inkorporation in die Makrophagen aufgelöst werden müssen. Die ^{45}Ca-Aktivität wurde dementsprechend im übrigen Skelett gefunden (7), was die Umsetzung über den Stoffwechsel beweist.

Wertung

Damit konnte von der Werkstoffseite aus gezeigt werden, warum die verschiedenen Präparate sich so differenziert verhalten:
Einzelne Präparate sind so niedrig oder so schnell gebrannt, daß sie keinerlei mechanische Festigkeit zeigen und deshalb im Organismus (oder in wäßrigen Lösungen im Schütteltest) zu Pulver zerfallen. Bei normal gebrannter Keramik kann starke Resorption in direkten Zusammenhang mit der Anwesenheit von TCP als Zweitphase gebracht werden. Wegen der Schwankungen der Stöchiometrie des Rohstoffs wurden in der Vergangenheit viele Präparate als HA-Keramik verkauft, die in Wirklichkeit eine Mischung von HA und TCP waren. Phasenreine TCP-Keramiken können dagegen auch mit sehr hoher Resorptionsresistenz gesintert werden, was an einem Handelspräparat durch langjährige experimentelle Beobachtung zu belegen ist.

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Danksagung

Die Phasendiagramme sind der Publikation „Phase Diagrams for Ceramists" entnommen, Amer. Ceram. Soc.

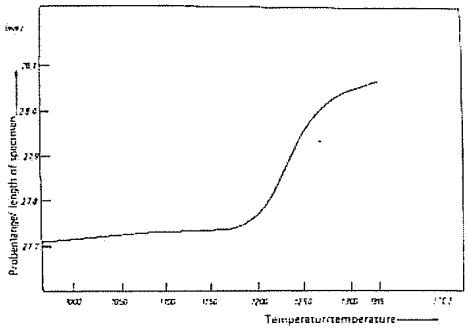

Abb. 5: Dilatometeraufnahme von TCP-Keramik: Längenänderung in Abhängigkeit von der Temperatur
Fig. 5: Dilatometric curve of a TCP-base ceramic: length as a function of temperature

ing to the results of dilatometric measurement, the transition occurs within a temperature range amounting to several hundred kelvin, and X-ray diffractometric spectra document the fact that most TCP-base ceramics still contain α-TCP as secondary phase at room temperature.

4. HA-base ceramics with a calcium deficit

As already mentioned, numerous ceramics have been found to contain too little calcium as a result of fluctuating raw-material compositions. Consequently, such ceramics contained noticeable amounts of TCP as a secondary phase and were vulnerable from the very start during cooling: since the expansion coefficients of α-TCP and HA do not match, there occurs a buildup of stress. This in addition to the volume surge undergone by TCP at the time of phase transition. Hence, two-phase HA-base ceramics are more vulnerable to microstructural disruption that are TCP-base ceramics, since, from the standpoint of sintering, it is easier to moderate stress levels in monophase TCP.

5. The effect of swelling minerals

Since TCP is not thermodynamically stable in water under normal circumstances, it undergoes phase transition to form HA, thereby absorbing water. Disregarding all other effects, that alone accounts for a 7.6% increase in volume. Roughly corresponding to the volumetric gain of freezing water, that phenomenon understandably disrupts the microstructure. This stands in agreement with the observation that Ca-phosphate ceramics suffer a pronounced loss of strength in aqueous solutions.

Isotope testing with ^{45}Ca

Isotope testing proved that the ceramic particles do not accumulate in soft tissue, most notably in the lymphatic nodes. This would indicate that the ceramic particles must dissolve after being incorporated into the macrophages. Accordingly, ^{45}Ca activity was detected in other parts of the skeleton [7], thus documenting the assumption of metabolic conversion.

Evaluation

From the standpoint of materials used, the experiments showed why the different preparations exhibit such different behavior:
Some preparations are fired at such low temperatures or so rapidly that they develop no mechanical strength at all and therefore disintegrate into powder upon being introduced into the organism (or even into an aquous solution for shake testing). In the case of normally fired ceramic material there is a direct connection between pronounced resorption and the presence of TCP as a secondary phase. Due to fluctuations in the stoichiometry of the raw material, many preparations have been marketed as HA-base ceramics, even though they actually comprised a mixture of HA and TCP. Pure TCP ceramics, however, can be sintered with very high resistance to resorption – as demonstrated by long-term experimental studies involving a commercial preparation.

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Please refer to German text.

Acknowledgment

The phase diagrams were borrowed from "Phase Diagrams for Ceramists", Amer. Ceram. Soc.

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Cerasorb®M – a new synthetic pure-phase β-TCP ceramic material in oral and maxillofacial surgery

An open study of 121 patients

DR. DR. FRANK PALM, GERMANY

DGZI
Deutsche Gesellschaft für Zahnärztliche Implantologie e.V.

dti] Dental Tribune International

ATTACHMENT II

Cerasorb®M – a new synthetic pure-phase β-TCP ceramic material in oral and maxillofacial surgery

An open study of 121 patients

author_Frank Palm, Germany

_**Bone substitutes** and bone regenerating materials are in high demand in dentistry and oral and maxillofacial surgery. Freshly harvested autogenous corticocancellous or cancellous bone chips are the most potent biologically. However, the additional surgical procedure for harvesting them, the potential donor site problems, the limited availability, the logistics needed and the potential forensic consequences complicate their exclusive use (Horch). A variety of bone substitutes, both biological and synthetic, are available as alternatives.

Chemically and thermally processed materials of animal (mostly bovine) origin are usually hydroxyapatites and are not resorbed or, at best, poorly resorbed. In the past few years synthetic materials containing only calcium and phosphate were developed. These are easily handled in the practical setting, economically attractive, effective, well tolerated, tissue compatible and devoid of local or systemic toxicity (Foitzik, Hille, Horch, Palti, Szabo, Zerbo). Unlike materials of biological origin, they do not carry any risks of transmitting infections and causing allergies (Hauschild, Hoenig).

They have long been used for filling bone defects such as those left by cystectomies or injuries, and are gaining increasing importance in implant dentistry because an adequate bone volume ensuring primary stability is key for placing root form implants. The bone volume needed for placing dental implants in the maxilla or mandible is at least 6 to 8 mm vertically and 5 mm transversally (Neukam). If this is not available, ridge augmentation is inevitable.

The author has gained extensive experience with developing and using synthetic bone regenerating materials over many years. In this article, experience with a new synthetic pure-phase β-TCP ceramic material are reported.

_Material and method

Between April 2003 and July 2005, 573 patients were treated with Cerasorb® M at the Department of Plastic Maxillofacial Surgery, Constance Medical Center, Germany. The material was mostly used in combination with autogenous bone. In 121 patients enrolled in an open prospective single-institution study, Cerasorb M was applied alone without any additional bone regenerating material. In 452 cases, Cerasorb M was combined with autogenous bone and occasionally Platelet Rich Plasma (PRP) for major ridge augmentations prior to implant placement.

Because of the poor comparability with patients treated with a mix of autogenous bone and a bone regenerating material, this report is confined to the patients who received Cerasorb M alone. The emphasis of this clinical study was on how well the new β-TCP performed clinically when compared to bone regenerating materials used in the past. There were 52 females and 69 males aged between 19 and 78 (median 59) years included in the study. The major indications were,

Fig. 1_ Preoperative OPG.
Fig. 2_ Condition after bilateral sinus lifting and simultaneous placement of three implants in the right and another three in the left maxilla, as well as two implants in the right mandible (see text).
Fig. 3_ Follow-up radiograph at 4 months. Note clearly visible resorption of bone regenerating material, which has largely been replaced by newly formed bone.

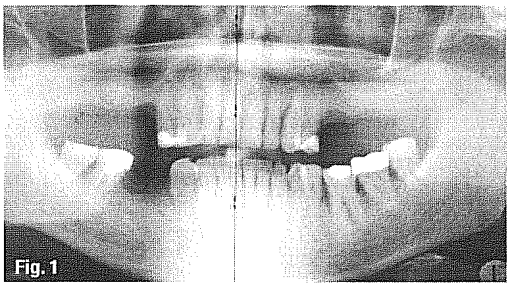
Fig. 1

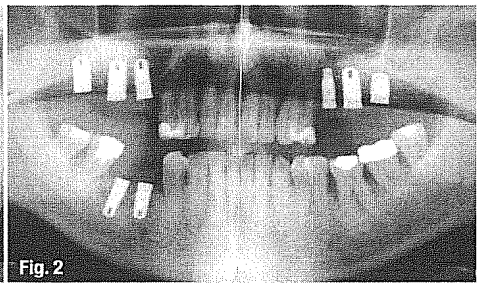
Fig. 2

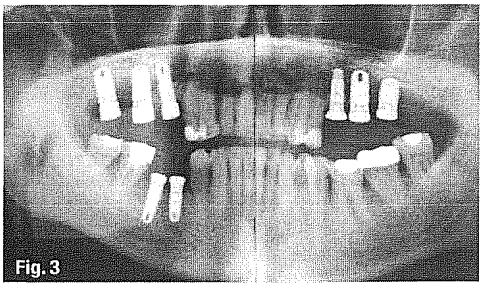
Fig. 3

1. Post-cystectomy defects (n = 64) in 63 patients
2. Sinus lifting (n = 79) in 58 patients.

Bone grafting was done with Cerasorb M (granules, granule size .1,000 to 2,000 µm, curasan AG, Germany), a new synthetic pure-phase β-TCP. This material is unique because of its interconnective open multiporosity and its polygonal granule structure. Its special micro-, meso- and macroporosity (total porosity is about 65%) produces an enhanced capillary effect and thus ensures cell nutrition and resorption from within. In numerous reports, extensively ramified macropore systems closed at their ends were shown to be colonized by microorganisms, which cannot be eliminated from the pore structure by cellular defense mechanisms (Bauer, Palm, Weibrich). Also, an optimal relationship between pore length and pore diameter was shown to be necessary for adequate nutrient transport. These insights were applied to the development of Cerasorb M.

Instead of an excessively interconnective macropore structure, the material has an interconnective micropore structure with interspersed meso- and macropores. This rules out ramification and closed ends. In addition, the large internal surface area and the high total porosity thus achieved enhance mechanical stability. As the polygonal granules interdigitate, undesirable micromovements are largely prevented. Still, the surface is smooth and well rounded without any sharp edges. Mixed with patient blood oozing from the defect, the material is easily applied and well retained. On account of the low density, less material is needed for the spacemaker function with less to be resorbed by the body.

Before placement, the viable bone is invariably freshened and the granules are always mixed with fresh blood from the site. Ibuprofen was routinely administered as an analgesic and anti-inflammatory. Perioperatively all patients received Augmentan® (amoxycillin and clavulanic acid), 2.2 g, by short infusion. Postoperative antibiotics were confined to patients with inflammatory lesions. These were given Augmentan postoperatively, followed by 875 mg b.i.d. for five days. All patients were followed up clinically and radiologically (OPG/DVT) at 3, 6, 9 and 12 months, and some of them for more than 2 years. Bone density was not routinely evaluated. Four months after sinus lifting, bone biopsies for histological analysis were obtained from 19 patients.

_Results

Packing the bone defects with the β-TCP granules proved to be easy and reliable throughout. Of the 121 patients included in the study, 83 had non-inflammatory lesions. None of them developed infections or showed poor wound healing, and the sutures were drawn after 10 to 14 days with the wounds clean and non-irritated. In two patients some of the material escaped through the mucosa during the late postoperative course. This did, however, not necessitate revision.

The remaining 28 patients had inflammatory lesions. One of them showed poor wound healing postoperatively and needed intravenous antibiotics (cephazolin and metronidazole) for three days. There was, however, no need to remove the grafting material. The other patients were routinely given Augmentan for antibiosis, as described earlier. Three defect sizes were distinguished by their largest radiographic diameter (Palm): up to 1.5 cm, 1.5 to 2.5 cm and more than 2.5 cm. For these, the radiologic outcome is reviewed below.

Of the patients with post-cystectomy defects, 26 fell into group I (defects of up to 1.5 cm in size). In 25 of them, the grafting material was completely replaced by bone at 3 months and in the remaining one at 6 months. Of the 25 patients with group II defects (largest diameter 1.5 to 2.5 cm), 23 showed complete replacement by bone at 6 months. In the remaining 2 patients, replacement was completed at 9 months. Twelve patients had group III defects (larger than 2.5 cm). In all of them the material was completely replaced by bone at 9 months. But evidence of bony ingrowth was already seen radiologically at 3 and 6 months. In view of the study design, radiographs and healing were evaluated in purely descriptive terms.

_Case report

Patient Sch. H. aged 68 years; bilateral sinus lift with Cerasorb M.

Under local anesthesia the patient (baseline OPG, Fig. 1) underwent bilateral sinus lifting and simultaneous placement of six tapered screw-vent implants in the maxilla and two tapered screw-vent implants in the mandible. The implants for the upper jaw had a diameter of 4.7 and 6.0 mm and a length of 11.5 mm to 13 mm; those for the lower jaw were 11.5 mm and 13 mm long

Fig. 4_ Follow-up radiograph at 14 months. Complete bony regeneration of the maxilla bilaterally. The bone regenerating material is no longer detectable.
Fig. 5_ Histology at 12 months. No evidence of TCP granules or their residues, numerous osteoblasts and formation of woven bone.
Fig. 6_ Histology at 12 months. Matrix of actively remodeling bone with some connective (scar) tissue.

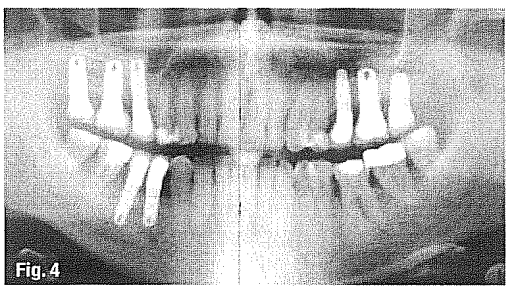
Fig. 4


Fig. 5


Fig. 6

and 4.5 mm wide. For sinus lifting, Cerasorb M with a granule size of 1,000 to 2,000 µm was used alone at a volume of 2 cc in the right maxilla and 1.5 cc in the left maxilla. As the periosteum was left intact during entry, membrane coverage was omitted.

Follow-up radiographs were recorded immediately after the procedure (Fig. 2), at 4 months (Fig. 3) and at 14 months (Fig. 4). The radiographs showed progressive obliteration of the defects by bone and simultaneous resorption of the grafting material. At 6 months the implants were exposed and loaded. On the last follow-up radiographs two years postoperatively, signs of mucosal irritation were absent and well developed bony structures were present at the grafted sites. During surgery for other reasons, bone biopsies were taken from the sites with the patient's consent. On histology 12 months after grafting, the bone regenerating material had completely been replaced by a matrix of actively remodeled bone with some connective (scar) tissue (Figs. 5, 6).

_Discussion

The ultimate goal of repairing bone defects is full recovery. In many reports addressing the problems of bone regeneration, autogenous bone is still considered to be the golden standard. However, when used alone, cancellous bone is often resorbed early. It is therefore not available long enough as a spacemaker and scaffold for osteoblasts to fill the defect with newly formed bone. Cortical bone, by contrast, is resorbed very slowly in a process that can take years in some instances.

Aside from these biological aspects, donor site morbidity is also a problem. Harvesting the material requires an additional surgical procedure, which uncontestedly inflicts added injury to the body and is associated with all but negligible complications (Banwart, Joshi, Niedhart).

A variety of biological and synthetic bone substitutes of varying chemical composition and biological origin has been available for some time now. Merten and coworkers impressively highlighted the differences between bone substitutes and bone regenerating materials (Merten). Resorption of the regenerating material with simultaneous new bone formation and sustained stability is key for the desired bone regeneration (Jerosch). With this in mind, pure-phase β-TCPs proved to be particularly useful. Among them, Cerasorb has been most widely studied clinically and is the best documented (eg, Foitzik, Hille, Horch, Hotz, Palti, Szabo, Wenz, Zerbo, Zijderfeld).

The inorganic, purely synthetic material has several distinct advantages over bone regenerating materials of biological origin: (1) precisely defined physicochemical and crystallochemical properties guaranteed in the production process, (2) constant batch quality and, as a result, (3) better predictability of the biological responses (Horch). Allografts and (mostly bovine) xenografts invariably carry certain residual risks and uncertainties for both the care providers and the patients. Reports in the literature have repeatedly referred to the potential and non-preventable transmission of BSE, foreign proteins and priones, and to potential reactions to bovine material (Hauschild, Hoenig, Horch). Potential immunologic or infective risks for patients have to be alerted when bovine materials are used (see Stuttgart High Court decision), which is not necessary when using β-TCP.

Another point to keep in mind is that non-resorbable or poorly and slowly resorbable materials may well fill defects, but their use neglects the physiologic dynamism of living bone. The jaw bone has a dynamism of its own and responds to normal masticatory forces acting on the natural dentition by resorption and remodeling. This is bound to fail if persistently present filling materials interfere or even prevent the process.

The synthetic pure-phase β-TCP Cerasorb M used in the patients under review is characterized by an open interconnective multiporosity and a polygonal granule structure. Thus, it almost matches autogenous bone. Its high total porosity of about 65% produces a capillary effect and forms the basis for cell nutrition and resorption from within the granules. Recent measurements documenting a phase purity of better than 99% for Cerasorb won the material a listing in the ICDD File as a worldwide standard for β-TCPs (ICDD).

Uneventful healing without irritations, ease of handling and well timed resorption depending on individual physiologic conditions with simultaneous formation of new bone are other points worth noting. All of this permits implant placement within no more than 4 to 6 months, an interval also needed by normal bone for new bone formation and regeneration. The consistent production quality guarantees reproducible high phase purity and reliable and predictable bone regeneration.

_Summary

The results of this study showed Cerasorb M to be an ideal synthetic bone regenerating material. Its porosity matches that of autogenous cancellous bone. It is readily resorbed within the limits of individual physiologic conditions so that new bone can be formed simultaneously and implants can be placed within no more than 4 to 6 months._

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Charakterisierung der Oberflächenmorphologie von Knochenersatzmaterialien mittels REM

Die Form und die Oberflächenmorphologie von Calciumphosphatgranulaten beeinflussen deren Eigenschaften als Knochenersatzmaterial. Daher wurden Form und Oberflächenmorphologie von klinisch verfügbaren Knochenersatzmaterialien auf Calciumphosphatbasis (Hydroxylapatite, Tricalciumphosphate und Biogläser) untersucht. Die rasterelektronenmikroskopische Untersuchung erfolgte in einem VP-SEM ohne Bedampfung bei 40, 100, 1000 und 3000facher Vergrößerung. Diese zeigte runde, ovale und vielkantig-bizarr geformte Granulate mit homogener oder heterogener Oberflächenmorphologie. Höhere Vergrößerungen ließen 5 Grade der Oberflächenrauhigkeit sinnvoll erscheinen. Die Granulatform sowie das Vorhandensein von Makroporen beeinflusst wesentlich die Größe des interpartikulären Raumes. Dies sind relevante Faktoren für die osteokonduktiven Eigenschaften der Knochenersatzmaterialien. Eine Bedeutung der Mikroporen bzw. der Oberflächenmikrorauhigkeit ist nicht hinsichtlich der Osteokonduktivität, sondern bezüglich der chemischen Löslichkeit und somit des Degradationsverhaltens des Knochenersatzmaterials zu vermuten. Bei Auswahl eines Knochenersatzmaterials auf Calciumphosphatbasis sollte auch die Granulatgrundform sowie die Oberflächenmorphologie Beachtung finden. Zum Ersatz größerer knöcherner Defekte eignen sich vielkantige, nahezu bizarr geformte Materialien mit hohem Anteil an Makroporen und somit entsprechend großer Oberflächenrauhigkeit, da für diese Indikation eine hohe Osteokonduktivität zu fordern ist. Bei kleineren Defekten im parodontalen Bereich mit einem höheren Kontaminationsrisiko erscheinen kugelähnlich geformte Granulate mit fehlender Makroposität (zur Reduktion von Bakteriennischen) sinnvoll.

SEM surface analysis of bone regeneration materials. *The particle shape and surface roughness has an effect on the properties of calcium phosphate granules as bone regeneration materials. The purpose of this study was to analyze the shape and surface homogeneity of various clinically available calcium phosphate bone regeneration materials (hydroxy apatites, tricalcium phosphates and bioglasses). SEM analysis was done without prior preparation of the specimens, and different magnification factors (40/100/1000/3000 x) were used. The results showed spherical, spheriodal, and bizarre particle shapes with a homogeneous or heterogeneous surface structure. At higher magnification, five different grades of surface homogeneity could be differentiated. Particle shape and presence of macropores are the main determinants of the resulting space between the calcium phosphate granules. These factors are important for the resulting osteoconductivity of the bone regeneration material. The micropores and the surface microroughness are assumed to influence the degradation characteristics rather than osteoconductivity. The shape of the granules and the surface structure are important criteria for the selection of a calcium phosphate bone regeneration material. For the repair of large bony defects, materials with bizarre particle shapes and a high proportion of macropores are needed. The use of materials with spherical particles and a minimal proportion of macropores can be recommended for minor bone defects in the periodontal area, where there is a greater risk for bacterial contamination.*

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